

REMARKS

With entry of this amendment, claims 1, 3-5, 12, 14, and 16-26 are pending in the application. Claims 2, 6-11, 13 and 15 were previously canceled, without prejudice. By this amendment, claims 1, 12, and 14 have been amended and new claims 24-26 added for clarity in accordance with the Office's suggestions. The amendments to claims 1, 12, and 14 reciting "an *S. typhi* Vi polysaccharide derived from *s. typhi* comprising an N-acetyl group" is supported in the specification, for example, at p. 6, lines 27-28. The introduction of new claims 24-26, reciting that the *S. typhi* Vi polysaccharide is covalently bound to the *Pseudomonas aeruginosa* recombinant exoprotein A "by means of a carboxylic acid dihydrazide linker" is supported throughout the specification and in the original claims (2, 13, and 15). No new matter has been added to the application. Entry of the amendments presented herein is respectfully requested.

Election/Restriction

The Office asserts that newly submitted claims 16-23 are directed to an invention that is "independent or distinct" from the invention originally claimed. In particular, the Office states that "[t]he previously examined claims were directed to the administration of a composition to any human, and the newly submitted claims are directed to the administration of the composition to humans of specific ages: 2-3 years old, 4-5 years old, 5-14 years old and adults." The Office further asserts that receipt of a prior action on the merits of the original claims supports constructive election of only the original claims. On this basis, the Office Action states that claims 16-23 are withdrawn from consideration. Applicants respectfully request reconsideration of the subject Restriction Requirement and constructive election.

The present response includes a Request for Continued Examination, which is believed to obviate the constructive election and avail Applicants of an opportunity to request reconsideration of the Restriction Requirement. In this regard, the original claims directed to vaccines and methods for use in all humans were clearly generic to the new claims presented in Applicants prior amendment directed to specific age groups. Therefore, at most, a species election with a prospect of reintroduction of

specific claims upon indication of an allowable species within the generic scope should be warranted. In addition, Applicants respectfully submit that the subject matter relating to specific age groups does not present an undue burden on the office with respect to searching and examining the application. On the contrary, such subject matter should already be within the scope of subject matter searched for the comprehensive genus originally presented directed to all human subjects—i.e., necessarily including the different age groups known to constitute targets for the claimed vaccine compositions and methods. For the foregoing reasons, reconsideration and withdrawal of the Restriction Requirement, and examination of all pending claims on the merits is earnestly solicited.

Rejections Withdrawn

Applicants acknowledge that the Office has reconsidered and withdrawn the prior rejection of claims 1-2, 5 and 12-14 under 35 U.S.C.102(a) as allegedly anticipated by Szu et al (December 8, 1997, different inventive entity), and that Szu et al (1997) has found by the Office not to represent prior art with respect to the current application.

Double Patenting

Claim 14 is rejected for alleged obviousness-type double patenting over claims 39 and 44 of U.S. Patent No. (US Pat. 5,738,855). The Office concedes that the conflicting claims are not identical, but asserts that they are not patentably distinct from each other “because the now claimed Vi antigen may be obtained from any source as long as it is characterized as S.typhi Vi antigen, and the allowed claims recite a species of Vi antigen that is synthetic, or immunologically equivalent obtained from a plant or fruit.” Applicants respectfully traverse.

The ‘855 patent is specifically directed to vaccines derived from “a plant or fruit polysaccharide” (see Title). The reference expressly teaches that the vaccine is an “O-acetylated plant, fruit or synthetic D-galacturonan, oligo saccharide or polysaccharide” (exemplified by O-acetylated pectin; “OAcPec”) conjugated to a carrier using a linking molecule.

The instant claims have been amended to specify that the subject embodiments of the invention incorporate “a molecular conjugate of the *S. typhi* Vi polysaccharide comprising an N-acetyl group and covalently bound through a carboxylic acid dihydrazide linker to *Pseudomonas aeruginosa* recombinant exoprotein A.” In contrast, the ‘855 patent teaches that “[t]he characteristics of OAcPec in comparison with Vi of *S. Typhi* is (sic) as follows:”

1) The M_1 of Vi (approx. 2×10^3 kD) is higher than that of OAcPec (approx. 400 kD; 2) the N-acetyl at C2 in the Vi is replaced by an O-acetyl in OAcPec and ; 3) OAcPec has <5% natural sugars and Vi had a nondetectable amount. (Col. 5, lines 1-7, underscore added).

By definition then, the O-acetylated plant, fruit or synthetic antigens disclosed in the ‘855 patent are distinct from the presently claimed subject matter employing *S. typhi* Vi polysaccharide comprising an N-acetyl group.

Not only does the ‘855 patent lack any disclosure of a useful vaccine conjugate incorporating a *S. typhi* Vi polysaccharide comprising an N-acetyl group, it expressly teaches away from this invention. In particular, the ‘855 inventors teach a specific preference for an O-acetylated derivative of a plant or fruit polysaccharide, which is antithetical to N-acetylation by virtue that this structural characteristic is disclosed as being “replaced” by O-acetylation.

In addition to this teaching, the ‘855 disclosure points away from N-acetylation as an antigenically important structural characteristic. In particular, the ‘855 specification compares the plant or fruit derived antigens disclosed and claimed to a native Vi molecule of *S. typhi*--emphasizing the distinct structural and functional differences related to O-acetylation versus N-acetylation. In this context, the ‘855 inventors state that:

[R]emoval of the O-acetyls removed most of the antigenicity and all of the immunogenicity of the Vi [23, 26]. The precise role of N-acetyl is not known as selective removal of the N-acetyl on Vi has not been accomplished. [col. 2, line 64-col.3, line 1, emphasis supplied].

Because the ‘855 patent teaches that O-acetyl removal abolishes “most of the antigenicity and all of the immunogenicity”, this would reasonably be interpreted to

suggest that the N-acetyl structure may have little or no role in immunogenicity of a synthetic Vi antigen. In addition, because removal of the N-acetyl had eluded practitioners in the art, efforts to further elucidate the role of the N-acetyl structure in Vi immunogenicity would likely have been considered unpredictable, or to be attended by a low expectation for success.

All of these teachings viewed collectively lead away from the instantly claimed subject matter. To propose that the teachings of the '855 patent would suggest the current invention is therefore contrary to the evidence of record. In fact, the '855 disclosure teaches directly away from the present invention, in several independent respects noted above. O-acetylation is disclosed as a preferred structural configuration, where N-acetylation is specifically excluded or "replaced". O-acetylation is also attributed as a critical structural feature for antigenicity and immunogenicity as compared to N-acetylation, which is in turn likely to be considered less significant or not significant at all to immunogenicity. Finally, further assessment of the importance of N-acetylation would have been considered challenging based on the notation in the '855 disclosure that this goal had not previously been accomplished.

Accordingly, the '855 patent clearly fails to anticipate or suggest the instantly claimed subject matter. With respect to obviousness-type double patenting, it is clear that no motivation or suggestion is provided in the record that would have led the ordinary artisan to modify the '855 fruit or plant polysaccharides by N-acetylation. On the contrary, the disclosure teaches directly away from such an undertaking. In this context, it is further noted that modification of the O-acetylated fruit or plant polysaccharide described in the '855 patent by synthetic methods, as proposed by the Office (i.e., to provide an N-acetyl structural group as instantly claimed) would also have been considered to be technically challenging, and, without clear motivation to undertake this modification, should not be considered obvious within the meaning of 35 U.S.C. § 103. Moreover, such a modification would certainly be considered unpredictable—particularly in the required context of providing an effective, antigenic and immunogenic Vi derivative as disclosed by Applicants. On this basis, the record fails to evince that a skilled artisan would have sought to modify the O-acetylated fruit or plant polysaccharide of the '855 patent to make an N-acetylated

derivative, with the requisite “reasonable expectation of success” for achieving an operable Vi antigen for use in the instantly claimed vaccine compositions and methods. This conclusion is well-founded on the evidence of record, including the teaching noted above that O-acetyl removal abolishes “most of the antigenicity and all of the immunogenicity” of synthetic Vi antigens.

The Office’s focus on alleged “immunological identity” between the subject matter of Applicants’ claims and that described in the ‘855 patent is inapposite to the review of double patenting issues. Applicants have shown explicit structural distinctions between the subject matter of the invention and the O-acetylated fruit or plant polysaccharide of the ‘855 patent. Applicants have also shown that the evidence of record teaches directly away from any proposed modification of the O-acetylated plant and fruit polysaccharides of the ‘855 patent by challenging and unpredictable attempts to make a synthetic N-acetylated derivative having antigenic and immunological activity. The noted structural and functional distinctions cannot be resolved by pointing to vague functional criteria pertaining to alleged “immunological identity.” Such a strained construction of the ‘855 teachings contravenes long-established legal authority governing enablement and written description, and is clearly contrary to the facts of record. Accordingly, the rejection of claim 14 for alleged obviousness-type double patenting over claims 39 and 44 of U.S. Patent No. 5,738,855 is respectfully submitted to be overcome.

Patentability Under 35 U.S.C. 102(e)

Claims 1, 3-5, 12, and 14 are rejected under 35 U.S.C. 102(e) as allegedly anticipated by Szu et al (Filing date: October 17, 1994; the ‘855 patent) for reasons of record in paper number 13, paragraph 6. The Office acknowledges the evidence presented in the record by Applicants, including Applicants’ assertion that the ‘855 patent teaches an O-acetylated pectin antigen that lacks the N-acetyl group of S.typhi Vi polysaccharide. However, the Office asserts that the previously claimed invention “would include synthetic Vi antigens with or without the N-acetyl group.” Further, the Office alleged that the ‘855 patent teaches a synthetic antigen “that comprises the antigenicity and immunogenicity of the Vi antigen . . . and would evidence immunological identity (citing Szu et al, ‘855, col. 2, lines 62-63; and claim 40).

Applicants respectfully traverse the stated grounds for rejection and submit that the instantly claimed invention is neither disclosed nor suggested by the Szu et al., '855 patent.

As an initial point, Applicants have amended the claims herein in accordance with the Office's suggestions--particularly to address the Office's stated objection that "the claims do not require the presence or absence of an N-acetyl group in the Vi antigen of the instant claims." The instant claims now clarify that the subject embodiments incorporate "a molecular conjugate of the *S. typhi* Vi polysaccharide comprising an N-acetyl group and covalently bound through a carboxylic acid dihydrazide linker to *Pseudomonas aeruginosa* recombinant exoprotein A." In contrast, the '855 patent is specifically directed to vaccines limited to an "O-acetylated plant, fruit or synthetic D-galacturonan, oligo saccharide or polysaccharide" (exemplified by O-acetylated pectin; "OAcPec") conjugated to a carrier using a linking molecule.

As noted above, the '855 patent further teaches that "[t]he characteristics of OAcPec in comparison with Vi of *S. Typhi* is (sic) as follows:"

- 1) The M_1 of Vi (approx. 2×10^3 kd) is higher than that of OAcPec (approx. 400 kD; 2) the N-acetyl at C2 in the Vi is replaced by an O-acetyl in OAcPec and ; 3) OAcPec has <5% natural sugars and Vi had a nondetectable amount. (Col. 5, lines 1-7, underscore added).

Thus, the O-acetylated plant, fruit or synthetic antigens disclosed in the '855 patent are clearly distinct from the presently claimed subject matter employing *S. typhi* Vi polysaccharide comprising an N-acetyl group.

Also in support of the instant rejection, the Office again focuses on alleged immunological identity between the subject matter of Applicants' claims and that described in the '855 patent. In particular, the Office asserts that the Vi polysaccharide derived from *S. typhi* "could comprise or not comprise the asserted structural component of an N-acetyl group as long as the polysaccharide derivative functions to induce an antibody directed to the Vi polysaccharide antigen." In addition, the Office contends that "[t]he synthetic saccharide (see claim 35) of Szu et

al '855, includes a synthetically synthesized Vi antigen (see Table 2, col. 14, line 45; claims 40 and 49) that would include the N-acetyl group of the native Vi polysaccharide because the immunogenic Vi epitope is defined to include this structure (see Szu et al., '855, col.2, lines 62-63)."

These assertions are contrary to the facts of record, and additionally fail to comport with controlling legal authority, as noted above. Briefly, the '855 patent lacks any disclosure of a useful vaccine conjugate incorporating a *S. typhi* Vi polysaccharide comprising an N-acetyl group. In fact, the '855 disclosure expressly teaches away from this subject matter. As noted above, the '855 specification teaches a specific preference for an O-acetylated derivative of a plant or fruit polysaccharide, which is directly contrasted to an N-acetylated derivative because the disclosure teaches that this structural element is "replaced" by O-acetylation.

Thus, Applicants have shown explicit structural distinctions between the subject matter of the invention and the O-acetylated fruit or plant polysaccharide of the '855 patent.

With respect to the Office's allegation that the synthetic antigen of the '855 patent "would include the N-acetyl group of the native Vi polysaccharide because the immunogenic Vi epitope is defined to include this structure", this statement is clearly contrary to the facts of record. The cited passage of the '855 patent relied upon by the Office pertains to the native Vi antigen, whereas the '855 patent teaches that antigenic and immunogenic, synthetic Vi antigens will be O-acetylated as opposed to N-acetylated. In this and other aspects, the '855 disclosure teaches directly away from N-acetylation as an antigenically important structural characteristic.

Briefly, as noted above, the '855 specification compares synthetic plant and fruit derived antigens to a native Vi molecule of *S. typhi*--emphasizing the distinct structural and functional differences related to O-acetylation versus N-acetylation. The '855 inventors expressly state that, in reference to the native antigen:

[R]emoval of the O-acetyls removed most of the antigenicity and all of the immunogenicity of the Vi [23, 26]. The precise role of N-acetyl is not known as selective removal of the N-acetyl on Vi has not been

accomplished. [col. 2, line 64-col.3, line 1, emphasis supplied].

Thus, the '855 patent teaches that O-acetyl removal abolishes "most of the antigenicity and all of the immunogenicity", which clearly contravenes any suggestion to N-acetylate the O-acetylated synthetic antigens presented in the reference, as proposed by the Office. In particular, the results noted by the '855 inventors would reasonably be interpreted to suggest that the presently claimed, N-acetyl structure may have little or no role in immunogenicity of a synthetic Vi antigen. Likewise, the fact that removal of the N-acetyl had previously eluded practitioners in the art, suggests that it would have been considered challenging or unpredictable to further elucidate the role of the N-acetyl structure in synthetic Vi antigen activity.

Based on this and other evidence of record, Applicants respectfully submit that the '855 patent teaches directly away from any proposed modification of O-acetylated plant and fruit polysaccharide antigens by N-acetylation. In fact, the '855 disclosure is limited to O-acetylated, plant or fruit polysaccharides. O-acetylation is presented as a preferred replacement structure for N-acetylation as occurs in the native Vi antigen model, and O-acetylation is specifically attributed as a critical structural feature for antigenicity and immunogenicity. Ablating this structure reportedly abolishes most of the antigenic potential and all of the immunogenic activity of a synthetic Vi antigen. Accordingly, N-acetylation would likely have been considered less significant, or not significant at all, to immunogenicity. Finally, further assessment of the importance of N-acetylation would have been considered challenging based on the notation in the '855 disclosure that this goal had not previously been accomplished.

On this basis, the '855 patent neither anticipates nor renders obvious the subject matter of the instant claims. The facts of record fail to establish a clear motivation or suggestion that would have led the ordinary artisan to modify the '855 fruit or plant polysaccharides by N-acetylation. On the contrary, the '855 disclosure teaches directly away from such an undertaking.

Applicants further submit that any attempts to modify an O-acetylated fruit or plant polysaccharide described of the '855 patent by synthetic methods to provide an

N-acetyl structural group, as instantly claimed would have been considered to be technically challenging. In addition, as suggested by the teachings of the '855 patent itself, such a modification would have been considered unpredictable—particularly when one considers the requirement that such a modified Vi derivative must be antigenic and immunogenic. Such activity would not have been predicted with the requisite “reasonable likelihood of success” for achieving Applicants’ compositions and methods, exhibiting the “particular results” disclosed—particularly considering that the '855 disclosure teaches that O-acetyl removal abolishes “most of the antigenicity and all of the immunogenicity” of synthetic Vi antigens.

To determine what constitutes a reasonable likelihood of success in this context, the Federal Circuit's predecessor court held in In re Gyurik, 201 USPQ 552, 557 (CCPA 1979) that:

An element in determining obviousness of a new chemical compound is the motivation of one having ordinary skill in the art to make it. That motivation is not abstract, but practical, and is always related to the properties or uses one skilled in the art would expect the compound to have, if made.

[T]he necessary motivation to make a claimed compound, and thus the prima facie case of obviousness, rises from the expectation that compounds similar in structure will have similar properties (id., at 557-558, emphasis supplied).

In the present case, the Office must complete its analysis of unexpected results by considering all evidence and properties of Applicants' claimed compositions and methods. In re Dillon, 16 USPQ2d 1897, 1901 (Fed. Cir. 1990). It is especially important that the Office consider "the particular results achieved by the new combination" Interconnect Planning Corp. v. Feil, 227 USPQ 543 (Fed. Cir. 1985).

Relating to this analysis, a patent applicant may rebut a *prima facie* case of unobviousness by showing 'unexpected results,' i.e., by establishing that the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected.

[T]hat which would have been surprising to a person of ordinary skill in the art would not have been obvious. The principle applies most often to less predictable fields, such as chemistry, where minor changes in a product or process may yield substantially different results. In re Soni, 34 USPQ2d 1684, 1687 (Fed. Cir. 1995).

In the instant case, the record fails to establish that a skilled artisan would have sought to modify the O-acetylated fruit or plant polysaccharide of the '855 patent to make an N-acetylated derivative, particularly with an expectation for achieving an operable Vi antigen for use in the presently claimed vaccine compositions and methods. Even if such a *prima facie* showing were established, however, Applicants claimed methods and vaccine formulations clearly provide "unexpected results" over the teachings of the prior art.

In this regard, the subject rEPA_{II} conjugate vaccines administered to 2- to 4-year olds significantly increased levels of anti-Vi antibodies compared to levels induced by rEPA_I). Even more surprisingly, this protection persisted even after 6 months post-inoculation. The rEPA_{II} conjugate resulted in greater than 90% protection against typhoid fever in the 2- to 5-year old age group that was studied in a phase III clinical trial. This high level of efficacy has now been shown to extend in the 2- to 5-year old age group for 27 months. Overall efficacy of the vaccine among the age groups tested in the clinical trial to date, after a nearly four year (46 month) period, was estimated to be an unprecedented 89% (confidence interval 76.0-97.0%). These additional data from a recently-submitted manuscript will be provided if the Office so requests.

The high level of efficacy of Applicants' vaccine compositions and methods, as disclosed in the specification and further validated by the ongoing phase III clinical trial results, is clearly unexpected in view of the teachings of the Szu et al., '855 patent, as discussed above. The Vi-rEPA_{II} conjugate vaccine of the instant invention

was substantially more effective than Vi-polysaccharide and the Vi-rEPA₁ conjugate (i.e., *S. typhi* Vi polysaccharide linked to rEPA with a SPDP linker) in adult humans, and was more effective than the Vi-rEPA₁ conjugate in all age groups. These results, including the unexpectedly high levels of antibodies in 2- to 4-year olds 6 months after incubation, are surprising and clearly not predicted based on the teachings of the '855 patent and other art of record. Such unexpected results are respectfully submitted to overcome any prima facie case as might be levied by the Office based on the facts of record.

In view of the foregoing evidence and authority, Applicants respectfully request that the rejection of the claims 1, 3-5, 12, and 14 under 35 U.S.C. 102(e) as allegedly anticipated by Szu et al (Filing date: October 17, 1994; the '855 patent) be reconsidered and withdrawn.

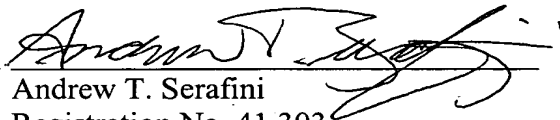
CONCLUSION

In view of the foregoing, Applicants believe that all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at (206) 332-1380.

Respectfully submitted,

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Andrew T. Serafini
Registration No. 41,303

Jeffrey J. King
Registration No. 38,515

Woodcock Washburn
999 Third Avenue, Suite 1606
Seattle, WA 98104
Telephone: 206/332-1380
Facsimile: 206/624-7317